

## REMARKS

Applicants have amended base Claim 9 to incorporate the limitation of Claim 10 (now canceled). In view of this amendment, Applicants have amended Claims 12 and 13 to change their dependency from Claim 10 to Claim 9 and have canceled now-redundant Claims 15, 17, and 19. Applicants have not altered the scope of the claims in any other manner.

### Rejection under 35 U.S.C. 103

Claims 9-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,194,418 ("Seitz et al"). Applicants respectfully traverse.

Seitz et al discloses certain aminosalicylamides, the preparation of which uses 4,6-dichloro-5-fluoropyrimidine (i.e., Applicants' formula (I)) as a starting material. See column 34, lines 23-30. Seitz et al teaches in general terms that 4,6-dichloro-5-fluoropyrimidine can be prepared by reaction of 5-fluoro-6-hydroxy-4(1H)-pyrimidinone (i.e., Applicants' formula (II)) in the so-called "process k" with a chlorinating agent and optionally in the presence of a diluent and/or a catalyst. E.g., column 34, lines 27-30. Among the many possible chlorinating agents disclosed in Seitz et al is phosgene. E.g., column 38, lines 12-18 (particularly line 15). It may be noted, however, that the only example of the disclosed process k uses phosphorous oxychloride as the halogenating agent (see Example (XIII) at column 48), which implies a preference for this halogenating agent. Among the many possible optional diluents are inert organic solvents such as aliphatic, alicyclic, or aromatic hydrocarbons; halogenated hydrocarbons; and nitriles. E.g., column 37, lines 1-10. Applicants note in this respect that Seitz et al discloses underivatized hydrocarbons, halogenated hydrocarbons, or cyano-substituted hydrocarbons (i.e., nitriles) but is silent with respect to other types of derivatized hydrocarbons, such as nitrobenzene (which is the solvent specified by Applicants). Among the many possible optional catalysts are tertiary amines (such as N,N-dimethylaminopyridine) and amides. E.g., column 38, lines 3-11 (particularly lines 8-9). It should be noted that although the tertiary amines are described as catalysts, Example (XIII) (mentioned above) describes the use of an equimolar amount of dimethylaminopyridine relative to the 5-fluoro-6-hydroxy-4(1H)-pyrimidinone, a larger amount than required for Applicants' claimed process (as shown in Applicants' examples and specified in Claim 18). Applicants note further that this relatively large amount of the amine base catalyst

has been described in U.S. Patent 6,255,486 as one of the drawbacks of the chlorination process described in Seitz et al. [The '486 patent is a counterpart of EP 1 077 210, which is mentioned in Applicants' specification at page 1, lines 10-18, as well as page 4, lines 5-7, with reference to the German counterpart of Seitz et al, DE-A1-19710609.]

Applicants note with respect to the choice of solvents that is not surprising that nitrobenzene is not among those specified by Seitz et al. Phosgenations in nitrobenzene are known to be problematic. In fact, phosgene is known to react with aromatic nitro compounds. For example, U.S. Patent 3,481,968 teaches that halogenated oxides of carbon such as phosgene react with aromatic nitro compounds such as nitrobenzene to form halogenated aromatic isocyanates. E.g., column 1, lines 15-18, as well as column 2, lines 38 et seq (especially line 57), and column 4, lines 11-20 (especially line 19). Similar teachings are found in an article by A. A. Ponomarenko in *Dopovidi Akademii Nauk Ukrains'koi RSR*, 6, 787-790 (1963) (Ukrainian language text with English abstract attached), which teaches that reaction of aromatic nitro compounds with chlorine compounds such as  $\text{COCl}_2$  (i.e., phosgene) leads to replacement of the nitro group by chlorine. See abstract at pages 789-790. [Applicants note that the copy of the Ponomarenko article obtained from the British Library omits a line of text and any headers from the top of each page. However, Applicants believe the remaining text is sufficiently complete for the purpose of this discussion.] Applicants therefore submit that those skilled in the art would expect nitrobenzene to be a completely unsuitable solvent for chlorinations using phosgene.

In the face of such teachings, Applicants nevertheless obtained very good yields of 4,6-dichloro-5-fluoropyrimidine by chlorinating the compound of their formula (II) with phosgene in nitrobenzene as solvent. See Examples 23-34 in Table A at pages 12-13 and 47 at page 16. Applicants note in particular Example 23, which shows that an acceptable yield is obtained using nitrobenzene as solvent even when no catalyst is used. This result is in stark contrast to the result obtained when Applicants attempted to chlorinate compound (II) with phosgene in chlorobenzene in the absence of catalyst. As can be seen by comparing Example 1 (chlorobenzene) with Example 23 (nitrobenzene), chlorination carried out in the absence of catalyst in chlorobenzene failed to produce isolable product, whereas chlorination under the

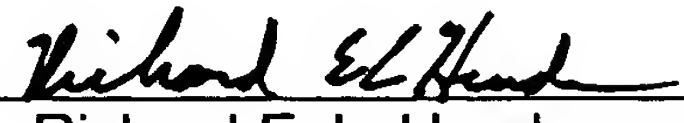
same conditions except for using nitrobenzene as solvent provided a 66% yield of the desired product. Even when a catalyst is included, chlorination with phosgene in nitrobenzene provided at least comparable and often better yields than chlorination in chlorobenzene. Compare, for example, Example 24 (93% using nitrobenzene) with Example 9 (74% using chlorobenzene), Example 28 (87% using nitrobenzene) with Example 3 (88% using chlorobenzene), Example 29 (88% using nitrobenzene) with Example 11 (86% using chlorobenzene), Example 30 (90% using nitrobenzene) with Example 12 (88% using chlorobenzene), and Example 31 (88% using nitrobenzene) with Example 2 (82% using chlorobenzene). Even Example 27, which was carried out similarly to Example 24 but with only one tenth the amount of the same catalyst, produced a higher yield than Example 9. These examples show that chlorobenzene, even though it can be used to good effect when a catalyst is present, never provides significant advantages over nitrobenzene and is often inferior to nitrobenzene, particularly in the absence of catalyst.

The boiling point of nitrobenzene provides another distinct advantage over chlorobenzene. Because 4,6-dichloro-5-fluoropyrimidine has a lower boiling point than nitrobenzene (ca. 170°C vs. ca. 210°C), the product advantageously distills off from the reaction medium before the solvent (as well as any bottoms), thereby greatly simplifying collection of product. On the other hand, because 4,6-dichloro-5-fluoropyrimidine has a higher boiling point than chlorobenzene (ca. 170°C vs. ca. 130°C), chlorobenzene must distill off before product can be collected.

In view of an unexpected combination of good yields and relatively easy distillation, Applicants submit that their claimed invention is unexpectedly superior to the method disclosed in Seitz et al and therefore respectfully submit that their claimed invention is not rendered obvious by Seitz et al.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

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